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Note

The synthesis of 2-(*aldo*-polyhydroxyalkyl)benzimidazoles as potential antineoplastic compounds

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Hirchberg, Gellhorn, and Gump[1] reported that "benzimidazole mustard" has antitumor activity in a variety of experimental, mouse-tumor systems, and Armaghan[2] showed that "5,6-dimethylbenzimidazole mustard" has pronounced antitumor activity in IRC 741 leukemia of Fischer rats. Baker and co-workers[3] pointed out that the most effective biological alkylating agents are those in which the carrier portions are either metabolites or antimetabolites. The carrier portions in Hirchberg and co-workers' and Armaghan's compounds may act either as purine antagonists or as vitamin B_{12} antagonists. It might be envisaged that certain benzimidazoles that do not bear biological alkylating groups may possess antineoplastic activity merely by acting as antimetabolites. Folkers and collaborators[4] have, in fact, reported that 5-methyl-2-(L-*arabino*-tetritol-1-yl)-benzimidazole has anticancer activity in the lymphosarcoma (6C3H-ED) test-system in mice.

Vargha's group showed that "D-mannitol mustard" is an effective antitumor substance[5], but "galactitol mustard" is inactive[3]. It therefore seemed feasible that 2-(*aldo*-polyhydroxyalkyl)benzimidazoles having the *manno* configuration might have significant anticancer activity. Dr. Nelson K. Richtmyer informed me that he had submitted 2-(D-*manno*-pentitol-1-yl)benzimidazole and 2-(5-deoxy-L-*manno*-pentitol-1-yl)benzimidazole for antitumor evaluation, and that the compounds had been found to be inactive[6]. Consequently, 2,2′-(D-*manno*-tetritol-1,4-diyl)bisbenzimidazole (**1**) was prepared by the procedure of Link and co-workers[7]. The dihydrochloride (N.S.C. 86172), the dipicrate (N.S.C. 92302), the hexaacetate (N.S.C. 93042), and the methanesulfonic salt (N.S.C. 96948) of **1** were screened for antineoplastic activity by the National Cancer Institute in Bethesda, Maryland. The compounds were all inactive in the leukemia 1210 mouse-system. In the P-1798 lymphosarcoma test-system, N.S.C. 86172 passed stage I of the sequential screen, but the activity was not confirmed on further testing. Although N.S.C. 93042 caused tumor regression in P-1798, it was judged inactive according to the National Cancer Institute's evaluation schedules. In the Lewis, lung carcinoma test-system, N.S.C. 92302 brought about tumor regression; the T/C value was, however, just outside the limit needed to warrant further testing*.

*Full details of the anticancer screening may be obtained from the National Cancer Institute, Bethesda, Maryland, U. S. A., by quoting the N.S.C. numbers.

The 5,5′-dichloro derivative of **1** was also synthesized; its methanesulfonic salt (N.S.C. 113987) was found inactive in the leukemia 1210 system. The National Cancer Institute found that N.S.C. 113987 is effective in deactivating adenine phosphoribosyltransferase[8]. Recently, N.S.C. 113987 has been found inactive in deactivating hypoxanthine–guanine phosphoribosyltransferase[8].

EXPERIMENTAL

General. — Solutions were evaporated at 40° *in vacuo*. Melting points are uncorrected. Microanalyses were performed by Dr. K. Führ at the University of Cape Town, South Africa.

Methanesulfonic salt of 2,2′-(D-manno-*tetritol-1,4-diyl*)*bisbenzimidazole.* — D-Mannitol was oxidized with nitric acid by Easterfield's method[9]. The oxidation mixture was then diluted with water (200 ml), the solution was made neutral with calcium carbonate, the excess of calcium carbonate was filtered off, and the filtrate was poured into ethanol (4 vol.). The fine precipitate resulting was collected by filtration, washed well with ethanol and then methanol, and dried. A suspension of this powder (24 g) in water (200 ml) was shaken with Amberlite IR-120 (H^+) ion-exchange resin until the solution was free from calcium ions. The mixture was filtered, and the filtrate was evaporated to a red syrup; this was treated with *o*-phenylenediamine (20 g) by the method of Link and co-workers[7]. The crude product (7.4 g) was purified by conversion into the dihydrochloride[7] (3.6 g) having m.p. 252–254° (dec.) and $[\alpha]_D$ −2° (c 0.18, water); lit.[7] m.p. 256–257°, $[\alpha]_D$ −1.3°.

Treatment of this dihydrochloride (1.8 g) with ammonium hydroxide[7] afforded the free base (1.2 g); this was suspended in M methanesulfonic acid (46 ml). On warming, a clear solution was obtained. After being kept for 24 h at room temperature, crystalline material had been deposited; this was filtered off, washed with acetone, and dried. The salt (1.5 g) had m.p. 258–260° (dec.).

Anal. Calc. for $C_{20}H_{26}N_4O_{10}S_2$: C, 43.9; H, 4.8; N, 10.3; S, 11.7. Found: C, 43.8; H, 5.1; N, 10.0; S, 12.0.

Methanesulfonic salt of 2,2′-(D-manno-*tetritol-1,4-diyl*)*bis(5-chlorobenzimidazole).* — 4-Chloro-*o*-phenylenediamine was treated with D-mannaric acid, and the 5,5′-dichloro derivative was isolated and purified as just described. A solution of the base in M methanesulfonic acid slowly deposited the crystalline methanesulfonic salt, m.p. 250–252° (dec.).

Anal. Calc. for $C_{20}H_{24}Cl_2N_4O_{10}S_2$: C, 39.0; H, 3.9; Cl, 11.5; N, 9.1; S, 10.4. Found: C, 38.3; H, 4.1; Cl, 11.3; N, 8.9; S, 10.1.

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